

Pulmonary alveolar proteinosis with lung squamous cell carcinoma

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by accumulation of periodic-acid-Schiff (PAS)-positive material in the alveolar space (1). Although the cause of this disease is unknown, functionally defective alveolar macrophages or defective clearance of intra-alveolar surfactant re-uptake by type 2 pneumocytes have been proposed by some investigators (2,3). In this context, PAP has been reported as a complication of certain diseases such as tuberculosis, haematological malignancy, interstitial pneumonitis or AIDS (4-8). To our knowledge, we report the first case of extensively developed PAP coexisting with lung squamous cell carcinoma.

Case Report

A 67-year-old man was admitted to a local hospital with a 2-month history of cough, white sputum, dyspnoea and fever. Chest X-ray and computed tomography (CT) showed a diffuse linear and reticular shadow with a high attenuation area (crazy-paving appearance) on both sides mainly in the lower lung fields. Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed. Milky effluent was obtained on BAL and alveoli were found to be filled with PAS-positive lipid on TBLB. These features established the diagnosis of PAP. The patient was treated with whole lung lavage (WLL) (9) for PAP. However, he developed severe hypoxaemia which prevented continuation of WLL therapy. At that stage, the patient was referred to our hospital for continuation of WLL using partial extra-corporeal circulation.

The past history and family history were not remarkable. He was a smoker with 2 packs of cigarettes daily for more than 40 years, and was a farmer with a negative occupational history. On physical examination, his height was 159 cm, body weight 48 kg, and a slight cyanosis was observed. Auscultation of the chest revealed fine crackles on the lower regions of the chest, bilaterally. The white

blood cell (WBC) count was 3600 mm^{-3} with 12% eosinophils. Laboratory tests showed an erythrocyte sedimentation rate (ESR) of 12 mm h^{-1} , and elevated positive C-reactive protein (CRP) (1.29 mg dl^{-1}), serum IgE (1211 U ml^{-1}), lactic dehydrogenase (LDH) (935 IU l^{-1}) and carcinoembryonic antigen (CEA) (41 ng ml^{-1}). Analysis of arterial blood gases on $101 \text{ min}^{-1} \text{ O}_2$ showed $\text{PaO}_2 = 10.8 \text{ kPa}$, $\text{PaCO}_2 = 5.5 \text{ kPa}$ and $\text{pH} = 7.379$. Chest X-ray and CT films taken in May 1994 showed a diffuse linear and reticular shadow with a high attenuation area in both lung fields together with a small nodular shadow in the right S^{10} area (Fig. 1). Whole right lung lavage using partial extra-corporeal circulation was performed successfully. The symptoms, laboratory tests and blood gas analysis improved following this procedure, and chest X-ray and CT film also showed a dramatic improvement and resolution of the mixed shadow in both lung fields (Fig. 2, top). As part of the routine follow-up, we repeated BAL examination, which showed a marked reduction of PAS-positive material in both lung fields in spite of a limiting whole lung lavage to the right side only. However, a single nodular shadow of approximately 1 cm in diameter at S^{10} in the right lung was observed in June 1994 (Fig. 2, bottom). TBLB was performed immediately to examine the nodular lesion. Examination of the biopsy material confirmed that the lesion was a squamous cell carcinoma. As the malignancy was classified as stage 1, right lower lobectomy was performed. A pathological diagnosis of moderately differentiated squamous cell carcinoma ($\text{T}_1\text{N}_0\text{M}_0$, stage 1) with residual focal areas of PAP was established.

Discussion

We reported a case of PAP with coexisting lung squamous cell carcinoma. PAP is a disease of unknown aetiology characterized by the deposition of PAS-positive material composed of lipid and protein within the alveoli (1). Several investigators have reported the presence of dysfunctional alveolar macrophages in patients with PAP. Golde and co-workers (2) showed that alveolar macrophages obtained from lavage fluid of patients with PAP had normal phagocytosis but a diminished capacity for killing yeasts. They suggested that the abnormal function of alveolar macrophages represented an acquired defect since normal

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FIG. 1. Computed tomography scan of the chest showing the diffuse linear and reticular shadow with a high attenuation area bilaterally and a small single nodular shadow on the S¹⁰ area of the right lung (bottom).

peripheral blood monocytes incubated with PAP lavage effluent developed morphological abnormalities similar to alveolar macrophages recovered from patients with PAP. More recent studies by Muller-Quernheim *et al.* (10) identified a protein in the lavage and serum of PAP patients capable of inhibiting the respiratory burst of normal blood cells. Based on this finding, they postulated that PAP is a manifestation of a suppressed function of alveolar macrophages. Furthermore, Athanassiadou *et al.* (11) reported that patients with primary lung cancer have a high number of functionally incompetent macrophages. They suggested that the process of primary lung malignancy exerts a local inhibitory effect on macrophages through the secretion of a chemical immune inhibitor. Based on these earlier studies, it is possible that PAP in our patient developed as a result of the initially unidentified lung squamous cell carcinoma.

On the other hand, Friemann *et al.* (12) have recently reported that both alveolar proteinosis and broncho-alveolar epithelial hyperplasia may possibly be obligatory preconditions for pulmonary tumour development in quartz-dust-treated rat lungs, suggesting that an unusual injury response to inhaled agents could also enhance tumour development. However, such mechanism is unlikely to explain the clinical course in our patient since his

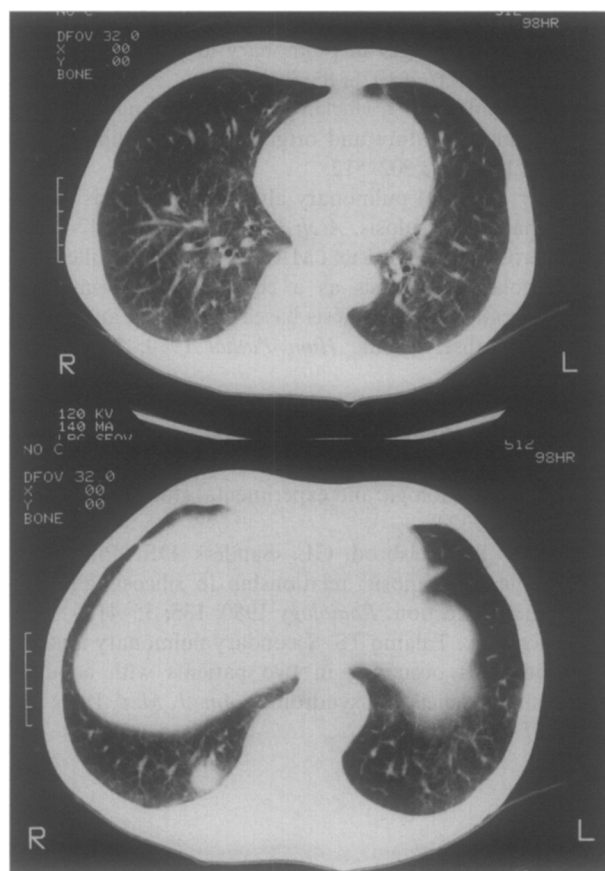


FIG. 2. Computed tomography scan of the chest showing improvement of the mixed shadows and development of a nodular shadow on the S¹⁰ area of the right lung (bottom) after whole right lung lavage using partial extra-corporeal circulation.

occupational history was negative. Recently, results of ultrastructural study have revealed a probable coexistence of PAP-type change in the vicinity of non-small-cell lung cancer, and it seems probable that the increased disintegration and desquamation of type 2 alveolar epithelial cells is an indirect cause of this change (13), consistent with the oldest theory of Kuhn *et al.* (14). Since PAP developed extensively in our patient, this may partly explain the residual focal areas of PAP adjacent to squamous cell carcinoma.

In conclusion, we have described the first case of extensively developed PAP associated with lung cancer. Although it is not yet clear whether the primary cause of PAP is the presence of dysfunctional alveolar macrophages, our case report indicates that PAP may develop in association with lung cancer, in addition to the reported association with haematological malignancies.

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